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Letter

Apremilast and adalimumab: a novel combination therapy for recalcitrant psoriasis

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Abstract

Psoriasis is a chronic immune-mediated inflammatory condition that affects 2-3% of the population. Apremilast was FDA-approved in March 2014 for the treatment of psoriatic arthritis and in September 2014 for the treatment of moderate to severe plaque psoriasis. Apremilast appears to have lower efficacy than some biologic agents such as adalimumab and ustekinumab, which achieve a PASI-75 in approximately 70% of patients after 12-16 weeks of therapy. However, its ease of administration as an oral agent coupled with a mild side effect profile make it an attractive option for psoriasis treatment. Herein, we present a patient with a 17-year history of plaque type psoriasis recalcitrant to topical, oral, and biologic mediations who attained near-complete remission after therapy with a combination of adalimumab and apremilast.

Keywords: biologic fatigue; phosphodiesterase-4; TNF- α

Introduction

Psoriasis is a chronic immune-mediated inflammatory condition that affects 2-3% of the population. We present a patient with a 17-year history of plaque type psoriasis recalcitrant to topical, oral, and biologic mediations who attained near-complete remission after therapy with a combination of adalimumab and apremilast.

Case synopsis

A 31-year-old man with a fifteen-year history of plaque type psoriasis presented to clinic after failing several therapies including topical therapy (including Class I topical steroids), phototherapy (narrow-band ultraviolet B [UVB] three times per week for several months), acitretin, and etanercept. At the time of presentation, the patient was using adalimumab (40 milligrams every other week) and clobetasol lotion for four years, which had initially controlled his psoriasis. However, in the last 6 months, the

patient noted steady recurrence of disease, primarily on his lower legs and trunk. Physical exam revealed scattered psoriatic plaques on the patient's chest, abdomen, back, and all four extremities, with more prominent involvement on the lower extremities. Apremilast (up-titrated to 30 mg twice per day) was added to his adalimumab therapy (at the standard therapeutic dose). Topical therapy remained unchanged. Four months since the combined use of apremilast and adalimumab therapy, the patient has noted significant improvement and is almost clear of psoriasis except for four, pea-sized residual lesions on each shin. Of note, the patient denies side effects of nausea, diarrhea, headache, or infection.

Discussion

Apremilast is an inhibitor of phosphodiesterase-4, which converts cyclic adenosine monophosphate (cAMP) to adenosine monophosphate (AMP). This results in the reduction of tumor necrosis factor- α (TNF- α), Interleukin-2 (IL-2), Interferon- α (IFN- α), several leukotrienes, and nitric oxide synthase [1, 2]. Apremilast was FDA-approved in March 2014 for the treatment of psoriatic arthritis and in September 2014 for the treatment of moderate to severe plaque psoriasis [3]. The medication's efficacy for plaque type psoriasis was demonstrated in two, 16-week, pivotal phase III studies, which involved a total of 1257 adults. The first trial showed that significantly more patients receiving apremilast achieved PASI-75 (33.1%) and PASI-50 (58.7%) versus placebo (5.3% and 17%; $P < .0001$) [4]. The second trial showed similar results: 29% of patients who received apremilast achieved PASI-75 versus 6% of patients who received placebo ($P < .0001$) [5]. Patients who had no prior exposure to oral or biologic agents showed significantly higher response rates with apremilast [4]. Overall, side effects of the medication are well tolerated; the most common adverse side effects included diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, and headache [4, 5].

The success of combination therapy with adalimumab and apremilast may relate to their distinct mechanisms of action. First, the effects of apremilast are intracellular whereas those of adalimumab are extracellular [1, 6]. Second, the effects of apremilast on the immune system are multifaceted. This is in contrast to the biologic agent adalimumab, which specifically targets TNF- α . Our patient improved after adding apremilast to gradually failing adalimumab monotherapy. This combined therapy would dampen immune hyperactivity at two different levels within the inflammatory cascade. Apremilast mainly has effects upstream, whereas adalimumab acts more downstream. Both adalimumab and apremilast are thought to decrease TNF- α . However, apremilast is also likely to inhibit other inflammatory pathways (e.g. T-helper [Th] 17 and Th22 pathways), which are important in the pathogenesis of psoriasis [7, 8]. Thus, it is probable that our patient had additive improvement in his disease after the addition of apremilast owing to its broader effects on inflammatory cytokines, and greater TNF- α suppression.

Apremilast appears to have lower efficacy than some biologic agents such as adalimumab and ustekinumab, which achieve a PASI-75 in approximately 70% of patients after 12-16 weeks of therapy [9-11]. However, its ease of administration as an oral agent coupled with a side effect profile that has yet to show clinical signs of immunosuppression or major organ toxicities, make it an attractive option for psoriasis treatment. We report the successful combined use of apremilast and a biologic agent for the treatment of a psoriasis patient who was experiencing biologic fatigue. Biologic fatigue has been demonstrated in 20-30% of patients who were followed for up to 3.9 years after receiving biologics [12]. The loss of response to adalimumab may involve anti-drug antibodies [12], a phenomenon that may have occurred in our patient after four years of therapy.

Our report suggests that one method for managing biologic fatigue is the addition of apremilast to a patient's current biologic therapy, which would require less blood work and possibly be safer than adding a traditional agent such as methotrexate. Though the safety of using adalimumab and apremilast together has not been formally studied, we felt that the combined use of these agents would likely be safe for two reasons. First, unlike adalimumab, apremilast has not shown clinical signs of immunosuppression, even after being tested in over 2000 patients [2, 4, 5, 7, 13-15]. Thus adding apremilast would not exacerbate the immunosuppression that may occur with adalimumab. Second, apremilast has shown drug-drug interactions with only four other medications (rifampin, phenobarbital, carbamazepine, phenytoin), all of which decrease the levels, and thus potential toxicities of apremilast [3]. However, more studies need to be done to determine the safety of using these agents together and clarify the efficacy of the combination in order to merit this approach for the management of psoriasis.

References

1. Schafer, P.H., et al., Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. *Cellular Signalling*, 2014. 26(9): p. 2016-2029. PMID: 24882690
2. Gottlieb, A.B., et al., An open-label, single-arm pilot study in patients with severe plaque-type psoriasis treated with an oral anti-inflammatory agent, apremilast. *Current Medical Research and Opinion*, 2008. 24(5): p. 1529-1538. PMID: 18419879
3. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206088s0001bl.pdf.
4. Reich, K., et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe psoriasis: 16-week results of a phase III, randomized, controlled trial (esteem 1). in *JOURNAL OF THE EUROPEAN ACADEMY OF*

DERMATOLOGY AND VENEREOLGY. 2013. WILEY-BLACKWELL 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.

5. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe psoriasis: 16-week results of a phase 3, randomized, controlled trial (ESTEEM 2). *Journal of the American Academy of Dermatology*, 2014. 70(5, Supplement 1): p. AB164. doi:10.1016/j.jaad.2014.01.682
6. Vergou, T., et al., Pharmacodynamics of TNF-alpha inhibitors in psoriasis. *Expert Rev Clin Pharmacol*, 2011. 4(4): p. 515-23. PMID: 22114860
7. Gottlieb, A.B., et al., Efficacy, tolerability, and pharmacodynamics of apremilast in recalcitrant plaque psoriasis: A phase II open-label study. *Journal of Drugs in Dermatology*, 2013. 12(8): p. 888-897. PMID: 23986162
8. Diani, M., G. Altomare, and E. Reali, T cell responses in psoriasis and psoriatic arthritis. *Autoimmun Rev*, 2014. PMID: 25445403
9. Gordon, K.B., et al., Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol*, 2006. 55(4): p. 598-606. PMID: 17010738
10. Leonardi, C.L., et al., Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*, 2008. 371(9625): p. 1665-74. PMID: 18486739
11. Papp, K.A., et al., Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*, 2008. 371(9625): p. 1675-84. PMID: 18486740
12. Levin, E.C., et al., Biologic fatigue in psoriasis. *J Dermatolog Treat*, 2014. 25(1): p. 78-82. PMID: 23875537
13. Kavanaugh, A., et al., Longterm (52-week) Results of a Phase III Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis. *J Rheumatol*, 2015. PMID: 25593233
14. Strand, V., et al., Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized, controlled study. *Health Qual Life Outcomes*, 2013. 11: p. 82. PMID: 23663752
15. Strand, V., et al., Patient-reported Health-related Quality of Life with apremilast for psoriatic arthritis: a phase II, randomized, controlled study. *J Rheumatol*, 2013. 40(7): p. 1158-65. PMID: 23588944